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| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | Jun 03 | New e-mail delivery for search results now available |
| NEWS 4 | Aug 08 | PHARMAMarketLetter(PHARMAML) - new on STN |
| NEWS 5 | Aug 19 | Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN |
| NEWS 6 | Aug 26 | Sequence searching in REGISTRY enhanced |
| NEWS 7 | Sep 03 | JAPIO has been reloaded and enhanced |
| NEWS 8 | Sep 16 | Experimental properties added to the REGISTRY file |
| NEWS 9 | Sep 16 | CA Section Thesaurus available in CAPLUS and CA |
| NEWS 10 | Oct 01 | CASREACT Enriched with Reactions from 1907 to 1985 |
| NEWS 11 | Oct 24 | BEILSTEIN adds new search fields |
| NEWS 12 | Oct 24 | Nutraceuticals International (NUTRACEUT) now available on STN |
| NEWS 13 | Nov 18 | DKILIT has been renamed APOLLIT |
| NEWS 14 | Nov 25 | More calculated properties added to REGISTRY |
| NEWS 15 | Dec 04 | CSA files on STN |
| NEWS 16 | Dec 17 | PCTFULL now covers WP/PCT Applications from 1978 to date |
| NEWS 17 | Dec 17 | TOXCENTER enhanced with additional content |
| NEWS 18 | Dec 17 | Adis Clinical Trials Insight now available on STN |
| NEWS 19 | Jan 29 | Simultaneous left and right truncation added to COMPENDEX, ENERGY, INSPEC |
| NEWS 20 | Feb 13 | CANCERLIT is no longer being updated |
| NEWS 21 | Feb 24 | METADEX enhancements |
| NEWS 22 | Feb 24 | PCTGEN now available on STN |
| NEWS 23 | Feb 24 | TEMA now available on STN |
| NEWS 24 | Feb 26 | NTIS now allows simultaneous left and right truncation |
| NEWS 25 | Feb 26 | PCTFULL now contains images |
| NEWS 26 | Mar 04 | SDI PACKAGE for monthly delivery of multifile SDI results |
| NEWS 27 | Mar 20 | EVENTLINE will be removed from STN |
| NEWS 28 | Mar 24 | PATDPAFULL now available on STN |
| NEWS 29 | Mar 24 | Additional information for trade-named substances without structures available in REGISTRY |
| NEWS 30 | Apr 11 | Display formats in DGENE enhanced |
| NEWS 31 | Apr 14 | MEDLINE Reload |
| NEWS 32 | Apr 17 | Polymer searching in REGISTRY enhanced |
| NEWS 33 | Jun 13 | Indexing from 1947 to 1956 added to records in CA/CAPLUS |
| NEWS 34 | Apr 21 | New current-awareness alert (SDI) frequency in WPIDS/WPINDEX/WPIX |
| NEWS 35 | Apr 28 | RDISCLOSURE now available on STN |
| NEWS 36 | May 05 | Pharmacokinetic information and systematic chemical names added to PHAR |
| NEWS 37 | May 15 | MEDLINE file segment of TOXCENTER reloaded |
| NEWS 38 | May 15 | Supporter information for ENCOMPPAT and ENCOMPLIT updated |
| NEWS 39 | May 16 | CHEMREACT will be removed from STN |
| NEWS 40 | May 19 | Simultaneous left and right truncation added to WSCA |
| NEWS 41 | May 19 | RAPRA enhanced with new search field, simultaneous left and right truncation |
| NEWS 42 | Jun 06 | Simultaneous left and right truncation added to CBNB |
| NEWS 43 | Jun 06 | PASCAL enhanced with additional data |

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NEWS 44  Jun 20  2003 edition of the FSTA Thesaurus is now available

NEWS EXPRESS  April 4 CURRENT WINDOWS VERSION IS V6.01a, CURRENT
              MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
              AND CURRENT DISCOVER FILE IS DATED 01 APRIL 2003
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 14:41:24 ON 24 JUN 2003

=> file reg
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:41:32 ON 24 JUN 2003
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STRUCTURE FILE UPDATES:   23 JUN 2003  HIGHEST RN 536496-82-9
DICTIONARY FILE UPDATES:  23 JUN 2003  HIGHEST RN 536496-82-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s p glycoprotein
        746054 P
         26321 GLYCOPROTEIN
L1         146 P GLYCOPROTEIN
                 (P(W)GLYCOPROTEIN)

=> file caplus
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       8.84       9.05
```

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FILE 'CAPLUS' ENTERED AT 14:42:03 ON 24 JUN 2003
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FILE COVERS 1907 - 24 Jun 2003  VOL 138 ISS 26
FILE LAST UPDATED: 23 Jun 2003  (20030623/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l1
L2           85 L1

=> s p glycoprotein
       2126568 P
         83926 GLYCOPROTEIN
L3        6487 P GLYCOPROTEIN
                 (P(W)GLYCOPROTEIN)

=> s protease inhibitor
         75708 PROTEASE
        414926 INHIBITOR
L4       11688 PROTEASE INHIBITOR
                 (PROTEASE(W)INHIBITOR)

=> e cancer
E1           13     CANCENTRINE/BI
E2            1     CANCENTRINEMETHINE/BI
E3       189703 --> CANCER/BI
E4            1     CANCER0/BI
E5            3     CANCER1/BI
E6            1     CANCER10/BI
E7            1     CANCER4/BI
E8            1     CANCERA/BI
E9            2     CANCERAND/BI
E10           1     CANCERARRAY/BI
E11          36     CANCERATION/BI
E12           1     CANCERB/BI

=> s e3
L5       189703 CANCER/BI

=> e neoplastic
E1            4     NEOPLAST/BI
E2            1     NEOPLASTIA/BI
E3        42911 --> NEOPLASTIC/BI
E4            2     NEOPLASTICA/BI
E5          338     NEOPLASTICALLY/BI
```

```
E6            1      NEOPLASTICCELL/BI
E7            1      NEOPLASTICDISEASES/BI
E8            8      NEOPLASTICITY/BI
E9            1      NEOPLASTICLLY/BI
E10           1      NEOPLASTICO/BI
E11           1      NEOPLASTICPROCESS/BI
E12          10      NEOPLASTICS/BI

=> s e3-e5
         42911 NEOPLASTIC/BI
             2 NEOPLASTICA/BI
           338 NEOPLASTICALLY/BI
L6       42966 (NEOPLASTIC/BI OR NEOPLASTICA/BI OR NEOPLASTICALLY/BI)

=> d his

     (FILE 'HOME' ENTERED AT 14:41:24 ON 24 JUN 2003)

     FILE 'REGISTRY' ENTERED AT 14:41:32 ON 24 JUN 2003
L1            146 S P GLYCOPROTEIN

     FILE 'CAPLUS' ENTERED AT 14:42:03 ON 24 JUN 2003
L2             85 S L1
L3           6487 S P GLYCOPROTEIN
L4          11688 S PROTEASE INHIBITOR
                  E CANCER
L5         189703 S E3
                  E NEOPLASTIC
L6          42966 S E3-E5

=> s l2 or l3
L7          6538 L2 OR L3

=> s l5 and l4
L8           356 L5 AND L4

=> s l8 and l7
L9             4 L8 AND L7

=> d l9 1-4

L9   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:679765  CAPLUS
TI   The protease inhibitor ritonavir inhibits the
     functional activity of the multidrug resistance related-protein 1 (MRP-1)
AU   Olson, Douglas P.; Scadden, David T.; D'Aquila, Richard T.; De Pasquale,
     Maria Pia
CS   AIDS Research Center, Massachusetts General Hosp., Harvard Med. Sch.,
     Boston, MA, USA
SO   AIDS (London, United Kingdom) (2002), 16(13), 1743-1747
     CODEN: AIDSET; ISSN: 0269-9370
PB   Lippincott Williams & Wilkins
DT   Journal
LA   English
RE.CNT  23    THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9   ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:651617  CAPLUS
DN   137:195065
TI   In vitro and in vivo modulation of MDR1/P-glycoprotein
     in HIV-infected patients administered highly active antiretroviral therapy
```

and liposomal doxorubicin
AU Lucia, Mothanje Barbara; Rutella, Sergio; Leone, Giuseppe; Larocca, Luigi Maria; Vella, Stefano; Cauda, Roberto
CS Department of Infectious Diseases, Catholic University, Rome, Italy
SO JAIDS, Journal of Acquired Immune Deficiency Syndromes (2002), 30(4), 369-378
CODEN: JJASFJ
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2000:614880 CAPLUS
DN 133:290617
TI The disposition of saquinavir in normal and **P-glycoprotein** deficient mice, rats, and in cultured cells
AU Washington, Carla B.; Wiltshire, Hugh R.; Man, Martha; Moy, Tina; Harris, Steve R.; Worth, Eric; Weigl, Paul; Liang, Zhenmin; Hall, David; Marriott, Lorraine; Blaschke, Terrence F.
CS Division of Clinical Pharmacology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
SO Drug Metabolism and Disposition (2000), 28(9), 1058-1062
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 1998:241719 CAPLUS
DN 129:12257
TI Overlapping substrate specificities of cytochrome P450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**
AU Zhang, Yuanchao; Guo, Xisheng; Lin, Emil T.; Benet, Leslie Z.
CS Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, 94143-0446, USA
SO Drug Metabolism and Disposition (1998), 26(4), 360-366
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l9 4 all

L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 1998:241719 CAPLUS
DN 129:12257
TI Overlapping substrate specificities of cytochrome P450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**
AU Zhang, Yuanchao; Guo, Xisheng; Lin, Emil T.; Benet, Leslie Z.
CS Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, 94143-0446, USA
SO Drug Metabolism and Disposition (1998), 26(4), 360-366
CODEN: DMDSAI; ISSN: 0090-9556

PB Williams & Wilkins
DT Journal
LA English
CC 1-2 (Pharmacology)
AB K02 (morpholine-urea-Phe-Hphe-vinylsulfone), a newly developed peptidomimetic, acts as a potent cysteine **protease inhibitor,** esp. of cathepsins B and L (which are assocd. with **cancer** progression) and cruzain (a cysteine protease of Trypanosoma cruzi, which is responsible for Chagas' disease). Here we investigated features of the disposition of K02 using in vitro systems, characterizing the interaction of the drug with human cytochrome P 450 (CYP) 3A and **P-glycoprotein** (P-gp), a mediator of multidrug resistance (MDR) to **cancer** chemotherapy and a counter-transporter in the intestine that limits oral drug bioavailability. P-gp functions as an ATP-dependent drug efflux pump to reduce intracellular cytotoxic concns. An HPLC assay was developed to analyze K02 and its metabolites formed in human liver microsomes. Three major primary metabolites were detd. by LC/MS/MS to be hydroxylated products of the parent compd. A rabbit anti-CYP3A polyclonal antibody (200 .mu.l antibody/mg microsomal protein) produced 75-94% inhibition of the formation of these three hydroxylated metabolites. Ketoconazole (5 .mu.M), a selective CYP3A inhibitor, produced up to 75% inhibition, whereas other CYP-specific inhibitors, i.e. quinidine (CYP2D6), 7,8-benzoflavone (CYP1A2), and sulfaphenazole (CYP2C9), showed no significant effects. An identical metabolite formation profile for K02 was obsd. with cDNA-expressed human CYP3A4 (Gentest). These data demonstrate that K02 is a substrate for CYP3A. Formation of 1'-hydroxymidazolam, the primary human midazolam metabolite, was markedly inhibited by K02 via competitive processes, which suggests the potential for drug-drug interactions of K02 with other CYP3A substrates. K02 significantly inhibited the photoaffinity labeling of P-gp with azidopine and LU-49888, a photoaffinity analog of verapamil. Transport studies with [14C]K02, using MDR1-transfected Madin-Darby canine kidney cell monolayers in the Transwell system, demonstrated that the basolateral-to-apical flux of K02 across MDR1-transfected Madin-Darby canine kidney cells was markedly greater than the apical-to-basolateral flux (ratio of 63 with 10 .mu.M [14C]K02). This suggests that K02 is also a P-gp substrate. These studies are important for formulating strategies to increase the absorption and/or decrease the elimination of K02 and to optimize its delivery to malignant cells and parasite-infected host cells.
ST pharmacokinetic P4503A glycoprotein P cysteine protease
IT Antitumor agents
Drug bioavailability
Liver
Microsome
Multidrug resistance
Pharmacokinetics
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)
IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)
IT Drug interactions
(pharmacokinetic; overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)
IT 9035-51-2, Cytochrome P 450, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(3A; overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 56-54-2, Quinidine 526-08-9, Sulfaphenazole 604-59-1, 7,8-Benzoflavone 65277-42-1, Ketoconazole 138674-34-7, Cysteine **protease inhibitor** 170111-23-6, K 02
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 59467-70-8, Midazolam
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 59468-90-5D, hydro 170111-23-6D, hydroxylated metabolites
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE


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=> g his
G IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

     (FILE 'HOME' ENTERED AT 14:41:24 ON 24 JUN 2003)

     FILE 'REGISTRY' ENTERED AT 14:41:32 ON 24 JUN 2003
L1           146 S P GLYCOPROTEIN

     FILE 'CAPLUS' ENTERED AT 14:42:03 ON 24 JUN 2003
L2            85 S L1
L3          6487 S P GLYCOPROTEIN
L4         11688 S PROTEASE INHIBITOR
                 E CANCER
L5        189703 S E3
                 E NEOPLASTIC
L6         42966 S E3-E5
L7          6538 S L2 OR L3
L8           356 S L5 AND L4
L9             4 S L8 AND L7

=> s s 16 and 14
MISSING OPERATOR S L6
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s 14 and 16
L10           83 L4 AND L6

=> s l10 and l7
L11            0 L10 AND L7

=> d his

     (FILE 'HOME' ENTERED AT 14:41:24 ON 24 JUN 2003)
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     FILE 'REGISTRY' ENTERED AT 14:41:32 ON 24 JUN 2003
L1           146 S P GLYCOPROTEIN

     FILE 'CAPLUS' ENTERED AT 14:42:03 ON 24 JUN 2003
L2            85 S L1
L3          6487 S P GLYCOPROTEIN
L4         11688 S PROTEASE INHIBITOR
                 E CANCER
L5        189703 S E3
                 E NEOPLASTIC
L6         42966 S E3-E5
L7          6538 S L2 OR L3
L8           356 S L5 AND L4
L9             4 S L8 AND L7
L10           83 S L4 AND L6
L11            0 S L10 AND L7

=> s hiv or retroviral or herpes or hhv
          49875 HIV
          13515 RETROVIRAL
          21443 HERPES
           1082 HHV
L12       81725 HIV OR RETROVIRAL OR HERPES OR HHV

=> s l12 and l4
L13        3094 L12 AND L4

=> s l13 and l7
L14          38 L13 AND L7

=> d l14 10-38

L14  ANSWER 10 OF 38  CAPLUS  COPYRIGHT 2003 ACS
AN   2002:1445  CAPLUS
DN   137:103470
TI   Multidrug resistance (MDR-1) expression in aids-related lymphomas
AU   Tulpule, Anil; Sherrod, Andy; Dharmapala, Dharshika; Young, Lillian L.;
     Espina, Byron M.; Sanchez, Maria Norilyn; Gill, Parkash S.; Levine,
     Alexandra M.
CS   Departments of Medicine and Pathology, University of Southern California
     Keck School of Medicine, Los Angeles, CA, USA
SO   Leukemia Research (2002), 26(2), 121-127
     CODEN: LERDD; ISSN: 0145-2126
PB   Elsevier Science Ltd.
DT   Journal
LA   English
RE.CNT  42    THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14  ANSWER 11 OF 38  CAPLUS  COPYRIGHT 2003 ACS
AN   2001:887744  CAPLUS
DN   136:193673
TI   Pharmacokinetic study of human immunodeficiency virus protease inhibitors
     used in combination with amprenavir
AU   Sadler, Brian M.; Gillotin, Catherine; Lou, Yu; Eron, Joseph J.; Lang,
     William; Haubrich, Richard; Stein, Daniel S.
CS   Glaxo Wellcome (now GlaxoSmithKline) Inc., Research Triangle Park, NC,
     27709-3398, USA
SO   Antimicrobial Agents and Chemotherapy (2001), 45(12), 3663-3668
     CODEN: AMACCQ; ISSN: 0066-4804
PB   American Society for Microbiology
```

DT Journal
LA English
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:711663 CAPLUS
DN 136:3505
TI Functional expression of **P-glycoprotein** in rat brain microglia
AU Lee, Gloria; Schlichter, Lyanne; Bendayan, Moise; Bendayan, Reina
CS Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON, Can.
SO Journal of Pharmacology and Experimental Therapeutics (2001), 299(1), 204-212
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:610087 CAPLUS
DN 135:352376
TI **HIV**-protease inhibitors contribute to **P-glycoprotein** efflux function defect in peripheral blood lymphocytes from **HIV**-positive patients receiving HAART
AU Lucia, Mothanje Barbara; Rutella, Sergio; Leone, Giuseppe; Vella, Stefano; Cauda, Roberto
CS Departments of Infectious Diseases and Hematology, Catholic University, Rome, Italy
SO JAIDS, Journal of Acquired Immune Deficiency Syndromes (2001), 27(4), 321-330
CODEN: JJASFJ
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:600077 CAPLUS
DN 136:288567
TI **P-glycoprotein** and transporter reduce **HIV protease inhibitor** uptake in CD4 cells: Potential for accelerated viral drug resistance?
AU Jones, Kevin; Bray, Patrick G.; Khoo, Saye H.; Davey, Ross A.; Meaden, E. Rhiannon; Ward, Stephen A.; Back, David J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3BX, UK
SO AIDS (London, United Kingdom) (2001), 15(11), 1353-1358
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:400334 CAPLUS
DN 136:144604

TI Differences in the intracellular accumulation of **HIV** protease inhibitors in vitro and the effect of active transport
AU Jones, Kevin; Hoggard, Patrick G.; Sales, Sean D.; Khoo, Saye; Davey, Ross; Back, David J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO AIDS (London, United Kingdom) (2001), 15(6), 675-681
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:319084 CAPLUS
DN 135:116507
TI Induction of **P-glycoprotein** and cytochrome P450 3A by **HIV** protease inhibitors
AU Huang, Liyue; Wring, Stephen A.; Woolley, Joseph L.; Brouwer, Kenneth R.; Serabjit-Singh, Cosette; Polli, Joseph W.
CS Division of Bioanalysis and Drug Metabolism, Glaxo SmithKline, Inc., Research Triangle Park, NC, 27709-3398, USA
SO Drug Metabolism and Disposition (2001), 29(5), 754-760
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE EOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE EORMAT

L14 ANSWER 17 OE 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:250584 CAPLUS
DN 135:204858
TI Assessment of active transport of **HIV** protease inhibitors in various cell lines and the in vitro blood-brain barrier
AU Van der Sandt, Inez C. J.; Vos, Catherine M. P.; Nabulsi, Lobna; Blom-Roosemalen, Margret C. M.; Voorwinden, Heleen H.; De Boer, Albertus G.; Breimer, Douwe D.
CS Leiden/Amsterdam Center for Drug Research, Division of Pharmacology, Leiden University, Leiden, 2300 RA, Neth.
SO AIDS (London, United Kingdom) (2001), 15(4), 483-491
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:240910 CAPLUS
DN 135:55434
TI **P-glycoprotein** limits oral availability, brain, and fetal penetration of saquinavir even with high doses of ritonavir
AU Huisman, Maarten T.; Smit, Johan W.; Wiltshire, Hugh R.; Hoetelmans, Richard M. W.; Beijnen, Jos. H.; Schinkel, Alfred H.
CS Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, Neth.
SO Molecular Pharmacology (2001), 59(4), 806-813
CODEN: MOPMA3; ISSN: 0026-895X
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal

LA English
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 19 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2001:114939 CAPLUS
DN 134:157539
TI **P-glycoprotein** modulator 10,11-methanodibenzosuberanes used with protease inhibitors for treating **HIV** infection
IN Wood, Alastair J. J.; Kim, Richard B.; Wilkinson, Grant R.
PA Vanderbilt University, USA
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2001010387 | A2 | 20010215 | WO 2000-US40588 | 20000807 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2000077574 | A5 | 20010305 | AU 2000-77574 | 20000807 |
| EP 1202737 | A2 | 20020508 | EP 2000-967364 | 20000807 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| PRAI US 1999-370266 | A | 19990809 | | |
| WO 2000-US40588 | W | 20000807 | | |

OS MARPAT 134:157539

L14 ANSWER 20 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2000:863216 CAPLUS
DN 134:141401
TI Inhibitory effect of human immunodeficiency virus protease inhibitors on multidrug resistance transporter P-glycoproteins
AU Shiraki, Nobuaki; Hamada, Akinobu; Yasuda, Kazuto; Fujii, Junko; Arimori, Kazuhiko; Nakano, Masahiro
CS Department of Pharmacy, Kumamoto University Hospital, Kumamoto, 860-8556, Japan
SO Biological & Pharmaceutical Bulletin (2000), 23(12), 1528-1531
CODEN: BPBLEO; ISSN: 0918-6158
PB Pharmaceutical Society of Japan
DT Journal
LA English
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 21 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2000:614880 CAPLUS
DN 133:290617
TI The disposition of saquinavir in normal and **P-glycoprotein** deficient mice, rats, and in cultured cells
AU Washington, Carla B.; Wiltshire, Hugh R.; Man, Martha; Moy, Tina; Harris, Steve R.; Worth, Eric; Weigl, Paul; Liang, Zhenmin; Hall, David; Marriott, Lorraine; Blaschke, Terrence F.
CS Division of Clinical Pharmacology, Department of Medicine, Stanford

University School of Medicine, Stanford, CA, USA
SO Drug Metabolism and Disposition (2000), 28(9), 1058-1062
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2000:393641 CAPLUS
DN 133:114577
TI Pharmacological inhibition of **P-glycoprotein** transport enhances the distribution of **HIV-1** protease inhibitors into brain and testes
AU Choo, Edna F.; Leake, Brenda; Wandel, Christoph; Imamura, Hitoshi; Wood, Alastair J. J.; Wilkinson, Grant R.; Kim, Richard B.
CS Departments of Medicine and Pharmacology, Division of Clinical Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232-6602, USA
SO Drug Metabolism and Disposition (2000), 28(6), 655-660
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 23 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2000:207641 CAPLUS
DN 132:216441
TI Significance of **P-glycoprotein** for the pharmacology and clinical use of **HIV** protease inhibitors
AU Huisman, Maarten T.; Smit, Johan W.; Schinkel, Alfred H.
CS Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, 1066 CX, Neth.
SO AIDS (London) (2000), 14(3), 237-242
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal; General Review
LA English
RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 2000:69563 CAPLUS
DN 132:146228
TI May the drug transporter **P glycoprotein** affect the antiviral activity of human immunodeficiency virus type 1 proteinase inhibitors? Comments
AU Srinivas, Ranga V.
CS Center for Scientific Review, National Institutes of Health, Bethesda, MD, 20892, USA
SO Antimicrobial Agents and Chemotherapy (2000), 44(2), 473-474
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 25 OF 38 CAPLUS COPYRIGHT 2003 ACS

AN 2000:42333 CAPLUS
DN 132:185324
TI Vitamin E-TPGS increases absorption flux of an **HIV** **protease inhibitor** by enhancing its solubility and permeability
AU Yu, Lawrence; Bridgers, Avis; Polli, Joseph; Vickers, Ann; Long, Stacey; Roy, Arup; Winnike, Richard; Coffin, Mark
CS Glaxo Wellcome, Inc., Research Triangle Park, NC, 27709, USA
SO Pharmaceutical Research (1999), 16(12), 1812-1817
CODEN: PHREEB; ISSN: 0724-8741
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 26 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:795653 CAPLUS
DN 132:30816
TI Methods and compositions using **P-glycoprotein** inhibitors for increasing penetration of **HIV** protease inhibitors
IN Brouwer, Kenneth Russell; Polli, Joseph William
PA Glaxo Group Limited, UK
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 9964001 | A2 | 19991216 | WO 1999-EP3827 | 19990603 |
| | WO 9964001 | A3 | 20000203 | | |
| | W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | AU 9945051 | A1 | 19991230 | AU 1999-45051 | 19990603 |
| | EP 1094814 | A2 | 20010502 | EP 1999-927848 | 19990603 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| PRAI | GB 1998-12189 | A | 19980605 | | |
| | WO 1999-EP3827 | W | 19990603 | | |

L14 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:692701 CAPLUS
DN 132:175298
TI Inhibition of the CYP3A4-mediated metabolism and **P-glycoprotein**-mediated transport of the **HIV-1** **protease inhibitor** saquinavir by grapefruit juice components
AU Eagling, V. A.; Profit, L.; Back, D. J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO British Journal of Clinical Pharmacology (1999), 48(4), 543-552
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell Science Ltd.
DT Journal

LA English
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 28 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:647476 CAPLUS
DN 132:146260
TI Modulation of **P-glycoprotein** function in human lymphocytes and Caco-2 cell monolayers by **HIV**-1 protease inhibitors
AU Profit, Louise; Eagling, Victoria A.; Back, David J.
CS Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK
SO AIDS (London) (1999), 13(13), 1623-1627
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 29 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:607911 CAPLUS
DN 132:27
TI Oral absorption of the **HIV** protease inhibitors: a current update
AU Williams, G. C.; Sinko, P. J.
CS College of Pharmacy, Rutgers - The State University of New Jersey, Piscataway, NJ, USA
SO Advanced Drug Delivery Reviews (1999), 39(1-3), 211-238
CODEN: ADDREP; ISSN: 0169-409X
PB Elsevier Science Ireland Ltd.
DT Journal; General Review
LA English
RE.CNT 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 30 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:548460 CAPLUS
DN 131:280972
TI Role of **p-glycoprotein** on the CNS disposition of amprenavir (141W94), an **HIV protease inhibitor**
AU Polli, Joseph W.; Jarrett, Jeanne L.; Studenberg, Scott D.; Humphreys, Joan E.; Dennis, Steven W.; Brouwer, Kenneth R.; Woolley, Joseph L.
CS Division of Bioanalysis and Drug Metabolism Glaxo Wellcome, Inc., Research Triangle Park, NC, 27709, USA
SO Pharmaceutical Research (1999), 16(8), 1206-1212
CODEN: PHREEB; ISSN: 0724-8741
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:508723 CAPLUS
DN 131:252148
TI Interactions of **HIV** protease inhibitors with ATP-dependent drug export proteins
AU Gutmann, Heike; Fricker, Gert; Drewe, Jurgen; Toeroek, Michael; Miller, David S.
CS Divisions of Gastroenterology and Clinical Pharmacology, Departments of Internal Medicine and Research, University Clinic (Kantonsspital and

Children's Hospital), Basel, Switz.
SO Molecular Pharmacology (1999), 56(2), 383-389
CODEN: MOPMA3; ISSN: 0026-895X
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1999:256246 CAPLUS
DN 131:53626
TI **HIV protease inhibitor** ritonavir: a more potent inhibitor of **P-glycoprotein** than the cyclosporine analog SDZ PSC 833
AU Drewe, Jurgen; Gutmann, Heike; Fricker, Gert; Torok, Michael; Beglinger, Christoph; Huwyler, Jorg
CS Department of Research and Department of Clinical Pharmacology, University Hospital, Basel, CH-4031, Switz.
SO Biochemical Pharmacology (1999), 57(10), 1147-1152
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:734897 CAPLUS
DN 130:133693
TI Interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein** (P-gp) in human cultured cells
AU Washington, Carla B.; Duran, George E.; Man, Martha C.; Sikic, Branimir I.; Blaschke, Terrence F.
CS Department of Medicine, Division of Clinical Pharmacology, Stanford University Medical Center, Stanford, CA, USA
SO Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1998), 19(3), 203-209
CODEN: JDSRET; ISSN: 1077-9450
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:625928 CAPLUS
DN 129:325717
TI Saquinavir, an **HIV protease inhibitor**, is transported by **P-glycoprotein**
AU Kim, Annice E.; Dintaman, Jay M.; Waddell, David S.; Silverman, Jeffrey A.
CS Drug Transport Division, AvMax, Inc., Berkeley, CA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(3), 1439-1445
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:538233 CAPLUS
DN 129:269846
TI Role of **P-glycoprotein** and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics
AU Wacher, Vincent J.; Silverman, Jeffrey A.; Zhang, Yuanchao; Benet, Leslie Z.
CS AvMax Inc., Berkeley, CA, 94710, USA
SO Journal of Pharmaceutical Sciences (1998), 87(11), 1322-1330
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal; General Review
LA English
RE.CNT 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:245898 CAPLUS
DN 129:12264
TI Active apical secretory efflux of the **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers
AU Alsenz, Jochem; Steffen, Hans; Alex, Rainer
CS Pharma Division, Preclinical Research Department, F. Hoffmann-La Roche Ltd, Basel, CH-4002, Switz.
SO Pharmaceutical Research (1998), 15(3), 423-428
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum Publishing Corp.
DT Journal
LA English
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:129660 CAPLUS
DN 128:252451
TI **HIV**-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug Transporter
AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.; Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.; Pastan, Ira; Dey, Saibal
CS Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD, 20892, USA
SO Biochemistry (1998), 37(11), 3594-3601
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English

L14 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:61905 CAPLUS
DN 128:200519
TI The drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors
AU Kim, Richard B.; Fromm, Martin F.; Wandel, Christoph; Leake, Brenda; Wood, Alastair J. J.; Roden, Dan M.; Wilkinson, Grant R.
CS Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232-6602, USA
SO Journal of Clinical Investigation (1998), 101(2), 289-294
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal

LA English
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L14 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:734897 CAPLUS
DN 130:133693
TI Interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein** (P-gp) in human cultured cells
AU Washington, Carla B.; Duran, George E.; Man, Martha C.; Sikic, Branimir I.; Blaschke, Terrence F.
CS Department of Medicine, Division of Clinical Pharmacology, Stanford University Medical Center, Stanford, CA, USA
SO Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1998), 19(3), 203-209
CODEN: JDSRET; ISSN: 1077-9450
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-5 (Pharmacology)
AB The anti-**HIV** protease inhibitors represent a new class of agents for treatment of **HIV** infection. Saquinavir, ritonavir, indinavir, and nelfinavir are the first drugs approved in this class and significantly reduce **HIV** RNA copy no. with minimal adverse effects. They are all substrates of cytochrome P 450 3A4, and are incompletely bioavailable. The drug transporting protein, **P-glycoprotein** (P-gp), which is highly expressed in the intestinal mucosa, could be responsible for the low oral bioavailability of these and other drugs which are substrates for this transporter. To det. whether these protease inhibitors are modulators of P-gp, we studied them in cell lines which do and do not express P-gp. Saquinavir, ritonavir and nelfinavir significantly inhibited the efflux of [3H]paclitaxel and [3H]vinblastine in P-gp-pos. cells, resulting in an increase in intracellular accumulation of these drugs. However, similar concns. of indinavir did not affect the accumulation of these anticancer agents. In photoaffinity labeling studies, saquinavir and ritonavir displaced [3H]azidopine, a substrate for P-gp, in a dose-dependent manner. These data suggest that saquinavir, ritonavir, and nelfinavir are inhibitors and possibly substrates of P-gp. Because saquinavir has a low bioavailability, its interaction with P-gp may be involved in limiting its absorption.
ST multidrug transporter **HIV protease inhibitor** uptake
IT Anti-AIDS agents
Drug bioavailability
(interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(multidrug transporter; interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)
IT 9035-51-2, Cytochrome P 450, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(3A4; interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)
IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)
IT 865-21-4, Vinblastine 33069-62-4, Paclitaxel
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(interaction of anti-**HIV** protease inhibitors with the multidrug transporter **P-glycoprotein**)
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

(1) Balani, S; Drug Metab Dispos 1995, V23, P266 CAPLUS
(2) Bruggemann, E; J Biol Chem 1989, V264, P15483
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L14 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:625928 CAPLUS

DN 129:325717
TI Saquinavir, an **HIV protease inhibitor**, is transported by **P-glycoprotein**
AU Kim, Annice E.; Dintaman, Jay M.; Waddell, David S.; Silverman, Jeffrey A.
CS Drug Transport Division, AvMax, Inc., Berkeley, CA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(3), 1439-1445
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 1-2 (Pharmacology)
AB This work investigated whether saquinavir is a substrate for the multidrug resistance transporter **P-glycoprotein** (P-gp), which may reduce the effective intracellular concn. of the drug. G185 cells, which highly express P-gp, were resistant to saquinavir-mediated cytotoxicity, and co-addn. of cyclosporine reversed this resistance. Saquinavir and saquinavir mesylate inhibited basolateral-to-apical transport of the fluorescent dye rhodamine 123 in a polarized epithelial transport assay, a result that suggests competition of these drugs for the P-gp transporter. Finally, the specific, directional transport of saquinavir and saquinavir mesylate was measured in an epithelial monolayer model. Transport in the basolateral-to-apical direction was 3-fold greater than apical-to-basolateral flux for both saquinavir and saquinavir mesylate and was blocked by co-incubation with the established P-gp-reversal agents cyclosporine and verapamil. These data provide evidence that saquinavir is a substrate for the P-gp transporter and suggest that this protein may affect intracellular accumulation of the drug and contribute to its poor oral bioavailability.
ST saquinavir transport multidrug resistance **P glycoprotein**
IT Multidrug resistance
(saquinavir transport by **P-glycoprotein** in relation to)
IT Biological transport
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT 127779-20-8, Saquinavir 149845-06-7, Saquinavir mesylate
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(multidrug resistance mediated by **P-glycoprotein** transport of)
IT 52-53-9, Verapamil 59865-13-3, Cyclosporin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(saquinavir transport by **P-glycoprotein** inhibition by)
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L14 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:538233 CAPLUS
DN 129:269846
TI Role of **P-glycoprotein** and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics
AU Wacher, Vincent J.; Silverman, Jeffrey A.; Zhang, Yuanchao; Benet, Leslie Z.
CS AvMax Inc., Berkeley, CA, 94710, USA
SO Journal of Pharmaceutical Sciences (1998), 87(11), 1322-1330
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 63
AB A review with 83 refs. Cytochrome P 450 3A4 (CYP3A4), the major phase I drug metabolizing enzyme in humans, and the MDR1 gene product **P-glycoprotein** (P-gp) are present at high concns. in villus tip enterocytes of the small intestine and share a significant overlap in substrate specificity. A large body of research both in vitro and in vivo has established metab. by intestinal CYP3A4 as a major determinant of the systemic bioavailability of orally administered drugs. More recently it has been recognized that drug extrusion by intestinal P-gp can both reduce drug absorption and modulate the effects of inhibitors and inducers of CYP3A-mediated metab. There is relatively little data regarding the effects of CYP3A and P-gp on peptide drugs; however, studies with the cyclic peptide immunosuppressant cyclosporine as well as peptidomimetics such as the **HIV-protease inhibitor** saquinavir (Invirase) and a new cysteine **protease inhibitor** K02 (Morpholine-Urea-Phe-Hphe-Vinyl sulfone; Axys Pharmaceuticals) provide some insight into the impact of these systems on the oral absorption of peptides.

ST review intestine **P glycoprotein** peptide absorption; cytochrome P450 peptide drug absorption review

IT Drug delivery systems
(oral; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

IT Intestine
Peptidomimetics
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

IT Peptides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

IT Biological transport
(uptake; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

IT 9035-51-2, Cytochrome p450, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(3A; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)

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L14 ANSWER 36 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:245898 CAPLUS
DN 129:12264
TI Active apical secretory efflux of the **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers
AU Alsenz, Jochem; Steffen, Hans; Alex, Rainer
CS Pharma Division, Preclinical Research Department, F. Hoffmann-La Roche Ltd, Basel, CH-4002, Switz.

SO Pharmaceutical Research (1998), 15(3), 423-428
CODEN: PHREER; ISSN: 0724-8741
PB Plenum Publishing Corp.
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 63
AB Purpose was to investigate in vitro the mechanisms involved in the gastro-intestinal absorption of the **HIV protease inhibitor,** saquinavir mesylate (Invirase.RTM.) whose oral bioavailability is low, variable, and significantly increased by co-administration with ritonavir, also an **HIV protease inhibitor** but with higher oral bioavailability. Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Both saquinavir and ritonavir showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory pathway), exceeding apical to basolateral transport (absorptive pathway) by factors of 50-70 and 15-25, resp. Active efflux was temp. dependent, saturable and inhibited by verapamil and cyclosporin A. Saquinavir and ritonavir decreased each other's secretory permeability and hence elevated their net transport by the absorptive pathway. Saquinavir and ritonavir are both substrates for an efflux mechanism in the gut, most likely **P-glycoprotein,** which acts as a counter-transporter for both drugs. Together with sensitivity to gut-wall metab. by cytochrome P 450 3A, this may partially account for the low and variable oral bioavailability of saquinavir in clin. studies and for its increased bioavailability after co-administration with ritonavir.
ST gastrointestinal absorption saquinavir ritonavir **P glycoprotein**
IT Animal cell line
(Caco-2; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Digestive tract
Drug bioavailability
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(drug; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(efflux; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Drug interactions
(pharmacokinetic; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT 149845-06-7, Invirase 155213-67-5, Ritonavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
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L14 ANSWER 37 OF 38 CAPLUS 
AN 1998:129660 CAPLUS
DN 128:252451
TI **HIV**-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug Transporter
AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.; Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.; Pastan, Ira; Dey, Saibal
CS Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD, 20892, USA
SO Biochemistry (1998), 37(11), 3594-3601
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-2 (Pharmacology)
AB The FDA approved **HIV**-1 protease inhibitors, ritonavir, saquinavir, and indinavir, are very effective in inhibiting **HIV** -1 replication, but their long-term efficacy is unknown. Since in vivo efficacy depends on access of these drugs to intracellular sites where **HIV**-1 replicates, we detd. whether these protease inhibitors are recognized by the MDR1 multidrug transporter (**P-glycoprotein**, or P-gp), thereby reducing their intracellular accumulation. In vitro studies in isolated membrane prepns. from insect cells infected with MDR1-expressing recombinant baculovirus showed that these inhibitors significantly stimulated P-gp-specific ATPase activity and that this stimulation was inhibited by SDZ PSC 833, a potent inhibitor of P-gp. Furthermore, photoaffinity labeling of P-gp with the substrate analog [125I]iodoarylazidoprazosin (IAAP) was inhibited by all three inhibitors. Cell-based approaches to evaluate the ability of these protease inhibitors to compete for transport of known P-gp substrates showed that all three **HIV**-1 protease inhibitors were capable of

inhibiting the transport of some of the known P-gp substrates but their effects were generally weaker than other documented P-gp modulators such as verapamil or cyclosporin A. Inhibition of **HIV**-1 replication by all three protease inhibitors was reduced but can be restored by MDR1 inhibitors in cells expressing MDR1. These results indicate that the **HIV**-1 protease inhibitors are substrates of the human multidrug transporter, suggesting that cells in patients that express the MDR1 transporter will be relatively resistant to the anti-viral effects of the **HIV**-1 protease inhibitors, and that absorption, excretion, and distribution of these inhibitors in the body may be affected by the multidrug transporter.

ST HIV1 **protease inhibitor** MDR1 multidrug transporter

IT Anti-AIDS agents
Antiviral agents
Human immunodeficiency virus 1
(**HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR1; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT Biological transport
(drug; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

L14 ANSWER 38 OF 38 CAPLUS COPYRIGHT 2003 ACS
AN 1998:61905 CAPLUS
DN 128:200519
TI The drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors
AU Kim, Richard B.; Fromm, Martin F.; Wandel, Christoph; Leake, Brenda; Wood, Alastair J. J.; Roden, Dan M.; Wilkinson, Grant R.
CS Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232-6602, USA
SO Journal of Clinical Investigation (1998), 101(2), 289-294
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Currently available **HIV**-1 protease inhibitors are potent agents in the therapy of **HIV**-1 infection. However, limited oral absorption and variable tissue distribution, both of which are largely unexplained, complicate their use. The authors tested the hypothesis that **P-glycoprotein** is an important transporter for these agents. The authors studied the vectorial transport characteristics of indinavir, nelfinavir, and saquinavir in vitro using the model **P-glycoprotein** expressing cell lines L-MDR1 and Caco-2 cells, and in vivo after i.v. and oral administration of these agents to mice with a disrupted mdr1a gene. All three compds. were found to be transported by **P-glycoprotein** in vitro. After oral administration,

plasma concns. were elevated 2-5-fold in mdr1a (-/-) mice and with i.v. administration, brain concns. were elevated 7-36-fold. These data demonstrate that **P-glycoprotein** limits the oral bioavailability and penetration of these agents into the brain. This raises the possibility that higher **HIV-1 protease inhibitor** concns. may be obtained by targeted pharmacol. inhibition of **P-glycoprotein** transport activity.

ST **P glycoprotein** HIV1 **protease inhibitor** bioavailability; absorption HIV1 **protease inhibitor P glycoprotein**; brain HIV1 **protease inhibitor P glycoprotein**

IT Animal cell line
(Caco-2; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Animal cell line
(L-MDR1; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Intestine
(colon; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Blood plasma
Blood-brain barrier
Brain
Digestive tract
Drug bioavailability
Drug metabolism
Heart
Kidney
Liver
Spleen
(drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Biological transport
(drug; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Intestine
(small; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT Biological transport
(uptake; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 159989-64-7, Nelfinavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV-1** protease inhibitors)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

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(FILE 'HOME' ENTERED AT 14:41:24 ON 24 JUN 2003)

FILE 'REGISTRY' ENTERED AT 14:41:32 ON 24 JUN 2003
L1 146 S P GLYCOPROTEIN

FILE 'CAPLUS' ENTERED AT 14:42:03 ON 24 JUN 2003
L2 85 S L1
L3 6487 S P GLYCOPROTEIN
L4 11688 S PROTEASE INHIBITOR
E CANCER
L5 189703 S E3
E NEOPLASTIC
L6 42966 S E3-E5
L7 6538 S L2 OR L3
L8 356 S L5 AND L4
L9 4 S L8 AND L7
L10 83 S L4 AND L6
L11 0 S L10 AND L7
L12 81725 S HIV OR RETROVIRAL OR HERPES OR HHV
L13 3094 S L12 AND L4
L14 38 S L13 AND L7

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---Logging off of STN---

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
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| FULL ESTIMATED COST | 91.73 | 100.78 |

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| CA SUBSCRIBER PRICE | -4.56 | -4.56 |

Connection closed by remote host

DN 129:12257
TI Overlapping substrate specificities of cytochrome P450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**
AU Zhang, Yuanchao; Guo, Xisheng; Lin, Emil T.; Benet, Leslie Z.
CS Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, CA, 94143-0446, USA
SO Drug Metabolism and Disposition (1998), 26(4), 360-366
CODEN: DMDSAI; ISSN: 0090-9556
PB Williams & Wilkins
DT Journal
LA English
CC 1-2 (Pharmacology)
AB K02 (morpholine-urea-Phe-Hphe-vinylsulfone), a newly developed peptidomimetic, acts as a potent cysteine **protease inhibitor**, esp. of cathepsins B and L (which are assocd. with **cancer** progression) and cruzain (a cysteine protease of Trypanosoma cruzi, which is responsible for Chagas' disease). Here we investigated features of the disposition of K02 using in vitro systems, characterizing the interaction of the drug with human cytochrome P 450 (CYP) 3A and **P-glycoprotein** (P-gp), a mediator of multidrug resistance (MDR) to **cancer** chemotherapy and a counter-transporter in the intestine that limits oral drug bioavailability. P-gp functions as an ATP-dependent drug efflux pump to reduce intracellular cytotoxic concns. An HPLC assay was developed to analyze K02 and its metabolites formed in human liver microsomes. Three major primary metabolites were detd. by LC/MS/MS to be hydroxylated products of the parent compd. A rabbit anti-CYP3A polyclonal antibody (200 .mu.l antibody/mg microsomal protein) produced 75-94% inhibition of the formation of these three hydroxylated metabolites. Ketoconazole (5 .mu.M), a selective CYP3A inhibitor, produced up to 75% inhibition, whereas other CYP-specific inhibitors, i.e. quinidine (CYP2D6), 7,8-benzoflavone (CYP1A2), and sulfaphenazole (CYP2C9), showed no significant effects. An identical metabolite formation profile for K02 was obsd. with cDNA-expressed human CYP3A4 (Gentest). These data demonstrate that K02 is a substrate for CYP3A. Formation of 1'-hydroxymidazolam, the primary human midazolam metabolite, was markedly inhibited by K02 via competitive processes, which suggests the potential for drug-drug interactions of K02 with other CYP3A substrates. K02 significantly inhibited the photoaffinity labeling of P-gp with azidopine and LU-49888, a photoaffinity analog of verapamil. Transport studies with [14C]K02, using MDR1-transfected Madin-Darby canine kidney cell monolayers in the Transwell system, demonstrated that the basolateral-to-apical flux of K02 across MDR1-transfected Madin-Darby canine kidney cells was markedly greater than the apical-to-basolateral flux (ratio of 63 with 10 .mu.M [14C]K02). This suggests that K02 is also a P-gp substrate. These studies are important for formulating strategies to increase the absorption and/or decrease the elimination of K02 and to optimize its delivery to malignant cells and parasite-infected host cells.
ST pharmacokinetic P4503A glycoprotein P cysteine protease
IT Antitumor agents
Drug bioavailability
Liver
Microsome
Multidrug resistance
Pharmacokinetics
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)
IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study);

PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT Drug interactions
(pharmacokinetic; overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(3A; overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 56-54-2, Quinidine 526-08-9, Sulfaphenazole 604-59-1, 7,8-Benzoflavone 65277-42-1, Ketoconazole 138674-34-7, Cysteine **protease inhibitor** 170111-23-6, K 02
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 59467-70-8, Midazolam
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

IT 59468-90-5D, hydro 170111-23-6D, hydroxylated metabolites
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(overlapping substrate specificities of cytochrome P 450 3A and **P-glycoprotein** for a novel cysteine **protease inhibitor**)

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD

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AN 1998:625928 CAPLUS
DN 129:325717
TI Saquinavir, an **HIV protease inhibitor**, is transported by **P-glycoprotein**
AU Kim, Annice E.; Dintaman, Jay M.; Waddell, David S.; Silverman, Jeffrey A.
CS Drug Transport Division, AvMax, Inc., Berkeley, CA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(3), 1439-1445
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 1-2 (Pharmacology)
AB This work investigated whether saquinavir is a substrate for the multidrug resistance transporter **P-glycoprotein** (P-gp), which may reduce the effective intracellular concn. of the drug. G185 cells, which highly express P-gp, were resistant to saquinavir-mediated cytotoxicity, and co-addn. of cyclosporine reversed this resistance. Saquinavir and saquinavir mesylate inhibited basolateral-to-apical transport of the fluorescent dye rhodamine 123 in a polarized epithelial transport assay, a result that suggests competition of these drugs for the P-gp transporter. Finally, the specific, directional transport of saquinavir and saquinavir mesylate was measured in an epithelial monolayer model. Transport in the basolateral-to-apical direction was 3-fold greater than apical-to-basolateral flux for both saquinavir and saquinavir mesylate and was blocked by co-incubation with the established P-gp-reversal agents cyclosporine and verapamil. These data provide evidence that saquinavir is a substrate for the P-gp transporter and suggest that this protein may affect intracellular accumulation of the drug and contribute to its poor oral bioavailability.
ST saquinavir transport multidrug resistance **P glycoprotein**
IT Multidrug resistance
(saquinavir transport by **P-glycoprotein** in relation to)
IT Biological transport
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT 127779-20-8, Saquinavir 149845-06-7, Saquinavir mesylate
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(multidrug resistance mediated by **P-glycoprotein** transport of)
IT 52-53-9, Verapamil 59865-13-3, Cyclosporin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(saquinavir transport by **P-glycoprotein** inhibition by)
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AN 1998:538233 CAPLUS
DN 129:269846
TI Role of **P-glycoprotein** and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics
AU Wacher, Vincent J.; Silverman, Jeffrey A.; Zhang, Yuanchao; Benet, Leslie Z.
CS AvMax Inc., Berkeley, CA, 94710, USA
SO Journal of Pharmaceutical Sciences (1998), 87(11), 1322-1330
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 63
AB A review with 83 refs. Cytochrome P 450 3A4 (CYP3A4), the major phase I drug metabolizing enzyme in humans, and the MDR1 gene product **P-glycoprotein** (P-gp) are present at high concns. in villus tip enterocytes of the small intestine and share a significant overlap in substrate specificity. A large body of research both in vitro and in vivo has established metab. by intestinal CYP3A4 as a major determinant of the systemic bioavailability of orally administered drugs. More recently it has been recognized that drug extrusion by intestinal P-gp can both reduce drug absorption and modulate the effects of inhibitors and inducers of CYP3A-mediated metab. There is relatively little data regarding the effects of CYP3A and P-gp on peptide drugs; however, studies with the cyclic peptide immunosuppressant cyclosporine as well as peptidomimetics such as the **HIV-protease inhibitor** saquinavir (Invirase) and a new cysteine **protease inhibitor** K02 (Morpholine-Urea-Phe-Hphe-Vinyl sulfone; Axys Pharmaceuticals) provide some insight into the impact of these systems on the oral absorption of peptides.
ST review intestine **P glycoprotein** peptide absorption; cytochrome P450 peptide drug absorption review
IT Drug delivery systems
(oral; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Intestine
Peptidomimetics
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Peptides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Biological transport
(uptake; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT 9035-51-2, Cytochrome p450, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(3A; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
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AN 1998:245898 CAPLUS
DN 129:12264
TI Active apical secretory efflux of the **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers
AU Alsenz, Jochem; Steffen, Hans; Alex, Rainer
CS Pharma Division, Preclinical Research Department, F. Hoffmann-La Roche Ltd, Basel, CH-4002, Switz.
SO Pharmaceutical Research (1998), 15(3), 423-428
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum Publishing Corp.
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 63
AB Purpose was to investigate in vitro the mechanisms involved in the gastro-intestinal absorption of the **HIV protease inhibitor**, saquinavir mesylate (Invirase.RTM.) whose oral bioavailability is low, variable, and significantly increased by co-administration with ritonavir, also an **HIV protease inhibitor** but with higher oral bioavailability. Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Both saquinavir and ritonavir showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory pathway), exceeding apical to basolateral transport (absorptive pathway) by factors of 50-70 and 15-25, resp. Active efflux was temp. dependent, saturable and inhibited by verapamil and cyclosporin A. Saquinavir and ritonavir decreased each other's secretory permeability and hence elevated their net transport by the absorptive pathway. Saquinavir and ritonavir are both substrates for an efflux mechanism in the gut, most likely **P-glycoprotein**, which acts as a counter-transporter for both drugs. Together with sensitivity to gut-wall metab. by cytochrome P 450 3A, this may partially account for the low and variable oral bioavailability of saquinavir in clin. studies and for its increased bioavailability after co-administration with ritonavir.
ST gastrointestinal absorption saquinavir ritonavir **P glycoprotein**
IT Animal cell line
(Caco-2; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Digestive tract
Drug bioavailability
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(drug; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(efflux; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Drug interactions
(pharmacokinetic; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT 149845-06-7, Invirase 155213-67-5, Ritonavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)

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DN 128:252451
TI **HIV**-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug Transporter
AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.; Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.; Pastan, Ira; Dey, Saibal
CS Laboratory of Cell Biology, National Cancer Institute, Bethesda, MD, 20892, USA
SO Biochemistry (1998), 37(11), 3594-3601
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
CC 1-2 (Pharmacology)
AB The FDA approved **HIV**-1 protease inhibitors, ritonavir, saquinavir, and indinavir, are very effective in inhibiting **HIV**-1 replication, but their long-term efficacy is unknown. Since in vivo efficacy depends on access of these drugs to intracellular sites where **HIV**-1 replicates, we detd. whether these protease inhibitors are recognized by the MDR1 multidrug transporter (**P-glycoprotein**, or P-gp), thereby reducing their intracellular accumulation. In vitro studies in isolated membrane prepns. from insect cells infected with MDR1-expressing recombinant baculovirus showed that these inhibitors significantly stimulated P-gp-specific ATPase activity and that this stimulation was inhibited by SDZ PSC 833, a potent inhibitor of P-gp. Furthermore, photoaffinity labeling of P-gp with the substrate analog [125I]iodoarylazidoprazosin (IAAP) was inhibited by all three inhibitors. Cell-based approaches to evaluate the ability of these protease inhibitors to compete for transport of known P-gp substrates showed that all three **HIV**-1 protease inhibitors were capable of inhibiting the transport of some of the known P-gp substrates but their effects were generally weaker than other documented P-gp modulators such as verapamil or cyclosporin A. Inhibition of **HIV**-1 replication by all three protease inhibitors was reduced but can be restored by MDR1 inhibitors in cells expressing MDR1. These results indicate that the **HIV**-1 protease inhibitors are substrates of the human multidrug transporter, suggesting that cells in patients that express the MDR1 transporter will be relatively resistant to the anti-viral effects of the **HIV**-1 protease inhibitors, and that absorption, excretion, and distribution of these inhibitors in the body may be affected by the multidrug transporter.
ST HIV1 **protease inhibitor** MDR1 multidrug transporter
IT Anti-AIDS agents
Antiviral agents
Human immunodeficiency virus 1
(**HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)
IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR1; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)
IT Biological transport
(drug; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)
IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)
IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

DN 128:252451

TI **HIV**-1 Protease Inhibitors Are Substrates for the MDR1 Multidrug Transporter

AU Lee, Caroline G. L.; Gottesman, Michael M.; Cardarelli, Carol O.; Ramachandra, Muralidhara; Jeang, Kuan-Teh; Ambudkar, Suresh V.; Pastan, Ira; Dey, Saibal

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ST HIV1 **protease inhibitor** MDR1 multidrug transporter

IT Anti-AIDS agents
Antiviral agents
Human immunodeficiency virus 1
(**HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT Multidrug resistance proteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MDR1; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT Biological transport
(drug; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir
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IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; **HIV**-1 protease inhibitors are substrates for the MDR1 multidrug transporter)

AN 1998:245898 CAPLUS
DN 129:12264
TI Active apical secretory efflux of the **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers
AU Alsenz, Jochem; Steffen, Hans; Alex, Rainer
CS Pharma Division, Preclinical Research Department, F. Hoffmann-La Roche Ltd, Basel, CH-4002, Switz.
SO Pharmaceutical Research (1998), 15(3), 423-428
CODEN: PHREEB; ISSN: 0724-8741
PB Plenum Publishing Corp.
DT Journal
LA English
CC 1-2 (Pharmacology)
Section cross-reference(s): 63
AB Purpose was to investigate in vitro the mechanisms involved in the gastro-intestinal absorption of the **HIV protease inhibitor**, saquinavir mesylate (Invirase.RTM.) whose oral bioavailability is low, variable, and significantly increased by co-administration with ritonavir, also an **HIV protease inhibitor** but with higher oral bioavailability. Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Both saquinavir and ritonavir showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory pathway), exceeding apical to basolateral transport (absorptive pathway) by factors of 50-70 and 15-25, resp. Active efflux was temp. dependent, saturable and inhibited by verapamil and cyclosporin A. Saquinavir and ritonavir decreased each other's secretory permeability and hence elevated their net transport by the absorptive pathway. Saquinavir and ritonavir are both substrates for an efflux mechanism in the gut, most likely **P-glycoprotein**, which acts as a counter-transporter for both drugs. Together with sensitivity to gut-wall metab. by cytochrome P 450 3A, this may partially account for the low and variable oral bioavailability of saquinavir in clin. studies and for its increased bioavailability after co-administration with ritonavir.
ST gastrointestinal absorption saquinavir ritonavir **P glycoprotein**
IT Animal cell line
(Caco-2; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Digestive tract
Drug bioavailability
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(drug; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Biological transport
(efflux; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT Drug interactions
(pharmacokinetic; active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)
IT 149845-06-7, Invirase 155213-67-5, Ritonavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(active apical secretory efflux of **HIV** protease inhibitors saquinavir and ritonavir in Caco-2 cell monolayers)

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(30) Wils, P; Biochem Pharmacol 1994, V48, P1528 CAPLUS

AN 1998:538233 CAPLUS
DN 129:269846
TI Role of **P-glycoprotein** and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics
AU Wacher, Vincent J.; Silverman, Jeffrey A.; Zhang, Yuanchao; Benet, Leslie Z.
CS AvMax Inc., Berkeley, CA, 94710, USA
SO Journal of Pharmaceutical Sciences (1998), 87(11), 1322-1330
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 63
AB A review with 83 refs. Cytochrome P 450 3A4 (CYP3A4), the major phase I drug metabolizing enzyme in humans, and the MDR1 gene product **P-glycoprotein** (P-gp) are present at high concns. in villus tip enterocytes of the small intestine and share a significant overlap in substrate specificity. A large body of research both in vitro and in vivo has established metab. by intestinal CYP3A4 as a major determinant of the systemic bioavailability of orally administered drugs. More recently it has been recognized that drug extrusion by intestinal P-gp can both reduce drug absorption and modulate the effects of inhibitors and inducers of CYP3A-mediated metab. There is relatively little data regarding the effects of CYP3A and P-gp on peptide drugs; however, studies with the cyclic peptide immunosuppressant cyclosporine as well as peptidomimetics such as the **HIV-protease inhibitor** saquinavir (Invirase) and a new cysteine **protease inhibitor** K02 (Morpholine-Urea-Phe-Hphe-Vinyl sulfone; Axys Pharmaceuticals) provide some insight into the impact of these systems on the oral absorption of peptides.
ST review intestine **P glycoprotein** peptide absorption; cytochrome P450 peptide drug absorption review
IT Drug delivery systems
(oral; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Intestine
Peptidomimetics
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Peptides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT Biological transport
(uptake; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
IT 9035-51-2, Cytochrome p450, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(3A; role of **P-glycoprotein** and cytochrome P 450 3A in limiting oral absorption of peptides and peptidomimetics)
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AN 1998:625928 CAPLUS
DN 129:325717
TI Saquinavir, an **HIV protease inhibitor**, is transported by **P-glycoprotein**
AU Kim, Annice E.; Dintaman, Jay M.; Waddell, David S.; Silverman, Jeffrey A.
CS Drug Transport Division, AvMax, Inc., Berkeley, CA, USA
SO Journal of Pharmacology and Experimental Therapeutics (1998), 286(3), 1439-1445
CODEN: JPETAB; ISSN: 0022-3565
PB Williams & Wilkins
DT Journal
LA English
CC 1-2 (Pharmacology)
AB This work investigated whether saquinavir is a substrate for the multidrug resistance transporter **P-glycoprotein** (P-gp), which may reduce the effective intracellular concn. of the drug. G185 cells, which highly express P-gp, were resistant to saquinavir-mediated cytotoxicity, and co-addn. of cyclosporine reversed this resistance. Saquinavir and saquinavir mesylate inhibited basolateral-to-apical transport of the fluorescent dye rhodamine 123 in a polarized epithelial transport assay, a result that suggests competition of these drugs for the P-gp transporter. Finally, the specific, directional transport of saquinavir and saquinavir mesylate was measured in an epithelial monolayer model. Transport in the basolateral-to-apical direction was 3-fold greater than apical-to-basolateral flux for both saquinavir and saquinavir mesylate and was blocked by co-incubation with the established P-gp-reversal agents cyclosporine and verapamil. These data provide evidence that saquinavir is a substrate for the P-gp transporter and suggest that this protein may affect intracellular accumulation of the drug and contribute to its poor oral bioavailability.
ST saquinavir transport multidrug resistance **P glycoprotein**
IT Multidrug resistance
(saquinavir transport by **P-glycoprotein** in relation to)
IT Biological transport
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT P-glycoproteins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(saquinavir transport by **P-glycoprotein** in relation to multidrug resistance)
IT 127779-20-8, Saquinavir 149845-06-7, Saquinavir mesylate
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(multidrug resistance mediated by **P-glycoprotein** transport of)
IT 52-53-9, Verapamil 59865-13-3, Cyclosporin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(saquinavir transport by **P-glycoprotein** inhibition by)
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AN 1998:61905 CAPLUS
DN 128:200519
TI The drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors
AU Kim, Richard B.; Fromm, Martin F.; Wandel, Christoph; Leake, Brenda; Wood, Alastair J. J.; Roden, Dan M.; Wilkinson, Grant R.
CS Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, 37232-6602, USA
SO Journal of Clinical Investigation (1998), 101(2), 289-294
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Currently available **HIV**-1 protease inhibitors are potent agents in the therapy of **HIV**-1 infection. However, limited oral absorption and variable tissue distribution, both of which are largely unexplained, complicate their use. The authors tested the hypothesis that **P-glycoprotein** is an important transporter for these agents. The authors studied the vectorial transport characteristics of indinavir, nelfinavir, and saquinavir in vitro using the model **P-glycoprotein** expressing cell lines L-MDR1 and Caco-2 cells, and in vivo after i.v. and oral administration of these agents to mice with a disrupted mdr1a gene. All three compds. were found to be transported by **P-glycoprotein** in vitro. After oral administration, plasma concns. were elevated 2-5-fold in mdr1a (-/-) mice and with i.v. administration, brain concns. were elevated 7-36-fold. These data demonstrate that **P-glycoprotein** limits the oral bioavailability and penetration of these agents into the brain. This raises the possibility that higher **HIV**-1 **protease inhibitor** concns. may be obtained by targeted pharmacol. inhibition of **P-glycoprotein** transport activity.
ST **P glycoprotein** HIV1 **protease inhibitor** bioavailability; absorption HIV1 **protease inhibitor P glycoprotein**; brain HIV1 **protease inhibitor P glycoprotein**
IT Animal cell line
(Caco-2; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors)
IT Animal cell line
(L-MDR1; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors)
IT Intestine
(colon; drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors)
IT Blood plasma
Blood-brain barrier
Brain
Digestive tract
Drug bioavailability
Drug metabolism
Heart
Kidney
Liver
Spleen
(drug transporter **P-glycoprotein** limits oral absorption and brain entry of **HIV**-1 protease inhibitors)
IT P-glycoproteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(drug transporter **P-glycoprotein** limits oral

absorption and brain entry of **HIV**-1 protease inhibitors)
IT Biological transport
(drug; drug transporter **P-glycoprotein** limits oral
absorption and brain entry of **HIV**-1 protease inhibitors)
IT Intestine
(small; drug transporter **P-glycoprotein** limits oral
absorption and brain entry of **HIV**-1 protease inhibitors)
IT Biological transport
(uptake; drug transporter **P-glycoprotein** limits
oral absorption and brain entry of **HIV**-1 protease inhibitors)
IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 159989-64-7, Nelfinavir
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(drug transporter **P-glycoprotein** limits oral
absorption and brain entry of **HIV**-1 protease inhibitors)
IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; drug transporter **P-glycoprotein** limits
oral absorption and brain entry of **HIV**-1 protease inhibitors)
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